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Case Report

Getting the diagnostic clue, role of MRI in the diagnosis of type 1 Glutaric aciduria in resource-limited settings ☆

Pradeep Raj Regmi, MD[a], *Aalok Kumar Yadav, MD*[a], *Bibek Koirala, MD*[a], *Shreelal Yadav, MD*[b], *Suraj Shrestha, MBBS*[c,*]

[a] *Department of Radiology, Tribhuvan University Teaching Hospital, Kathmandu, Nepal*
[b] *Department of Radiology, Malangawa Hospital, Sarlahi, Nepal*
[c] *Maharajgunj Medical Campus, Institute of Medicine, Kathmandu, Nepal*

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ABSTRACT

Glutaric aciduria type 1 is a rare autosomal recessive disorder caused by a deficiency of glutaryl-CoA dehydrogenase, which is the key mitochondrial enzyme involved in the final degradation of lysine, L-hydroxylysine, and L-tryptophan. It is an inherited organic acidemia characterized by macrocephaly and dystonia, which results in high morbidity and mortality. In resource-limited countries like Nepal, where enzyme assays are not available, MRI has a great role to play in supporting diagnosis in such situations. Here, we present 2 cases of glutaric aciduria type 1 in brothers from the same parent that were diagnosed by MRI, and subsequent diet modification and L-carnitine therapy led to improvement of clinical symptoms.

Introduction

Glutaric aciduria type 1 is a rare neurometabolic autosomal recessive disorder caused by a glutaryl-CoA dehydrogenase (GCDH) deficiency, [1,2] associated with encephalopathic crisis and severe extrapyramidal symptoms [1]. The GCDH gene is localized on chromosome 19p13.2. It encodes a flavin adenine dinucleotide-dependent mitochondrial matrix protein that is involved in the degradative metabolism of lysine, L-hydroxylysine, and L-tryptophan [2]. Macrocephaly, frontotemporal brain atrophy, and acute encephalopathic episodes characterize it, with striatal necrosis followed by dystonia [1]. Affected patients may develop normally up to 1-2 years of age; macrocephaly is a common finding and precedes the onset of neurological manifestations. If untreated, 90% of patients between 3 and 36 months of age suffer regression and severe dystonic-dyskinetic disorder [3,4]. Cognitive functions are relatively spared [4].

In resource-limited countries like Nepal, where enzyme assays are not available, MRI has a great role to play in supporting diagnosis in such situations. We present 2 siblings with

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* Corresponding author.
E-mail address: multisurazz@gmail.com (S. Shrestha).

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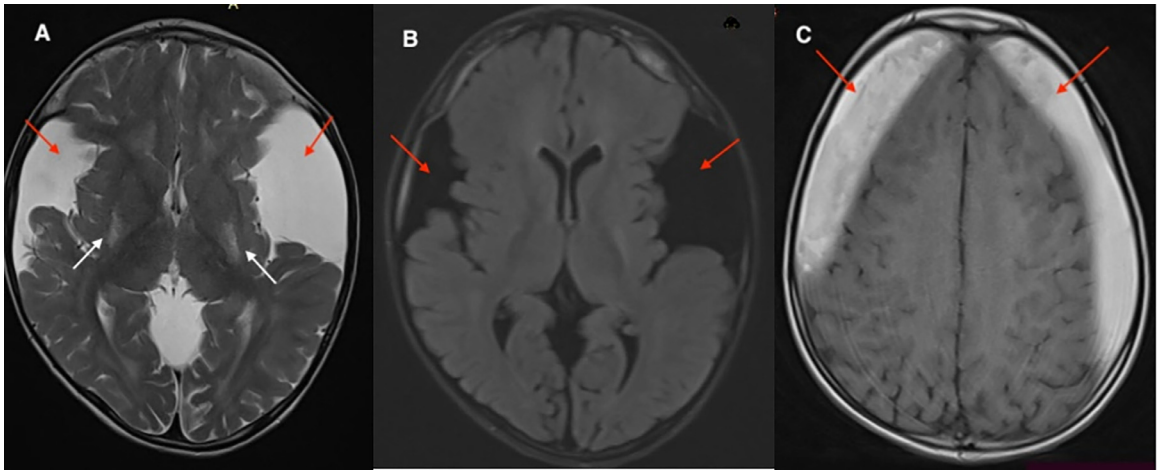

Fig. 1 – (A) Axial T2 MRI and (B) Axial FLAIR MRI shows widening of the bilateral sylvian cisterns (red arrows) and T2 high signal intensity within the bilateral lentiform nucleus (white arrows in A), (C) Axial T1 MRI shows symmetrical high signal intensity subdural collection suggesting sub-acute hematoma (red arrows).

typical magnetic resonance imaging (MRI) findings of glutaric aciduria type 1.

Case presentation

Case 1

A 6-year-old boy presented to pediatric out-patient department (OPD) with complaints of unsatisfactory right upper limb and bilateral lower limb movement along with unclear voice since birth. On examination, the head circumference (HC) was 53.5 cm (above the 95th percentile), the sensory system was intact, and on motor examination, power was decreased (right upper limb = 3/5, right lower limb = 4/5, left upper limb = 4/5, and left lower limb = 4/5), tone was decreased in all limbs, and dysarthria was present. Cranial nerves and reflexes were normal. The rest of the examination was unremarkable. There was no evidence of rib and extremity bone fractures, retinal hemorrhage, or skin bruises.

Routine lab tests (complete blood count, liver function test, renal function test, urine analysis) were within the normal limit. The patient was subjected to an MRI brain which revealed enlarged bilateral sylvian fissure and temporal lobe CSF spaces and T2 prolongation in bilateral basal ganglia and bilateral subdural hematoma (Fig. 1). Based on the above clinical features and MRI findings, glutaric aciduria-1 was suspected. Urinary tests for glutaric acid and 3-hydroxyglutaric acid were not done because of the unavailability of tests in our country. The patient was placed on lysine diet restriction and supplementation of L-carnitine, which showed improvement in the neurological symptoms of the child.

Case 2

This patient was the younger brother of the first patient (belonging to the same parent), i.e., 11 months old who presented with an inability to sit and a large head. On examination, HC was 48 cm (>95th percentile), the anterior fontanelle was open, the child was unable to sit with support, and there was no crawling or creeping present. The tone was decreased, but the cranial nerves and reflexes were intact. The rest of the examination was unremarkable. Routine lab tests (complete blood count, liver function test, renal function test, routine urinary analysis) were within the normal limit. The patient was subjected to an MRI of the brain, which revealed prominent bilateral Sylvian cisterns and subarachnoid spaces of bilateral temporal lobes and high T2 signal intensity in bilateral globus pallidus (Fig. 2).

Based on the above clinical features, typical MRI findings, and similar features in his elder brother (which explain the genetic basis of the disease), the child was diagnosed with glutaric aciduria type 1. The child was placed on dietary restriction of lysine, and oral L-carnitine was prescribed with physiotherapy. On subsequent follow-up visits, the child is improving.

Clinical discussion

Glutaric aciduria type 1 is a rare autosomal recessive disorder caused by a deficiency of glutaryl-CoA dehydrogenase, which is the key mitochondrial enzyme involved in the final degradation of lysine, L-hydroxylysine, and L-tryptophan. It is an inherited organic acidemia characterized by macrocephaly and dystonia, which results in high morbidity and mortality. In countries with resource-limited settings where enzymatic and gene mutation analysis are not available, MRI could be a great tool in diagnosis. In our cases, both cases present with macrocephaly, enlargement of the Sylvian fissure, and deep nuclei signal abnormalities. Macrocephaly, along with an enlarged bilateral Sylvian fissure and prominent CSF spaces, are major abnormalities that help to suspect the diagnosis of glutaric aciduria Type 1 [5]. MRI is not diagnostic, however with the typical and characteristic features explained in literature, it can be strongly suspected [6–8]. In this disease process, the

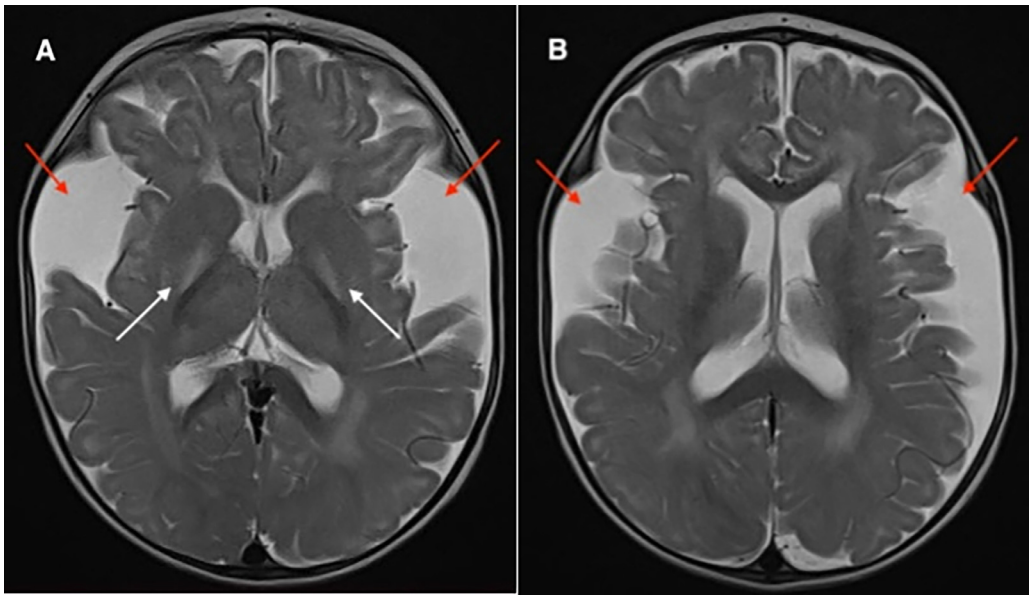

Fig. 2 – (A) Axial T2 MRI and (B) Axial FLAIR MRI shows a widening of the bilateral sylvian cisterns (red arrows) and T2 high signal intensity within the bilateral globus pallidus (white arrow in A) along with widening of the bilateral sylvian cisterns and subarachnoid spaces.

enlarged CSF spaces and prominent bilateral Sylvian fissures (bat wing sign) are due to neuronal hypoplasia rather than neuronal atrophy. MRI of patient 1 also showed high signal intensity within the bilateral lentiform nucleus in T2-weighted imaging, and T2-high signal intensity changes are also seen in patient 2. These deep nuclei changes are due to edema in acute stages, leading to T2 high signal intensity, whereas in chronic stages, there will be atrophy of these deep nuclei, giving permanent T2 high signal intensity changes [6–8]. Subdural hematomas seen in this disease process are due to cerebral atrophy leading to the tearing of the bridging vein, which can cause bleeding in subdural spaces spontaneously or due to minor trauma [8]. MRI of the brain in type 2 glutaric aciduria shows a T2-weighted prolongation in the corpus striatum, putamen, caudate nucleus, middle cerebral peduncles, and splenium of the corpus callosum [9].

The imaging differentials for this case could be benign enlargement of subarachnoid spaces of infancy (BESS), non-accidental injury (NAT), other entities causing macrocephaly and white matte changes like Canavan disease, Alexander disease, and Vander knaap disease. In BESS, there will be symmetrical prominent subarachnoid spaces in fronto-temporal lobes. However, bat wing sign as well as abnormal changes in the bilateral basal ganglia will be absent. In NAT, there will be suggesting history as well as subdural hemorrhages. However, the anatomical developmental abnormalities will be absent in NAT. Canavan disease have macrocephaly along with extensive areas of diffuse white matter T2/FLAIR high signal intensity. In child with Alexandar disease show frontal predominance of the T2/FLAIR white matter signal intensity. In Vander knap disease, there will be megalencephaly, diffuse T2/FLAIR white matter high signal intensity along with subcortical cysts in bilateral temporal lobes [7,8].

For the confirmation of the diagnosis, enzyme analysis like levels of glutaric acid and 3-hydroxyglutaric acid could be done in urine or blood, but this was not done in our cases because of the unavailability of these tests in our country. However, diagnosis was confirmed by similar MRI findings in both siblings, with improvement in clinical outcome with restriction of lysine and tryptophan in diet and supplementation of L-carnitine. Early diagnosis is very important in this disease process to prevent long-term neurological complications like neuroencephalitic crises and neurological damages by diet restriction and L-carnitine supplementation [10].

Conclusion

In resource-limited countries, where enzyme assays are not available, MRI has a great role to play in supporting diagnosis of glutaric aciduria.

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Ethical approval

Case reports are exempt from ethical approval at the Institute of Medicine, Tribhuvan University Teaching Hospital, Nepal.

Patient consent

Written informed consent was obtained from the patient's parents for publication of this case report and accompanying

images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

CRediT authorship contribution statement

Pradeep Raj Regmi: Conceptualization, Data curation, Supervision, Writing – review & editing. **Aalok Kumar Yadav:** Conceptualization, Data curation, Writing – review & editing. **Bibek Koirala:** Data curation, Writing – original draft, Writing – review & editing. **Shreelal Yadav:** Data curation, Writing – original draft, Writing – review & editing. **Suraj Shrestha:** Writing – original draft, Writing – review & editing.

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